REVIEW

Difficult situations in anticoagulation after stroke: between Scylla and Charybdis

George Ntaios[a] *and Gregory Y.H. Lip*[b,c]

Purpose of review
A significant proportion of stroke patients is treated with anticoagulants for secondary stroke prevention. Often, in such patients, stroke physicians are required to make difficult clinical decisions when confronted with the dilemma to choose between the risk of thromboembolism and the risk of bleeding. This article focuses on three common anticoagulant-related situations, where the stroke physician needs to find the delicate balance between the two risks.

Recent findings
Three typical case vignettes are presented and the associated dilemmas are discussed: a patient with an anticoagulant-related intracranial hemorrhage: would you restart anticoagulation?, an anticoagulated patient with a previous stroke because of atrial fibrillation is scheduled for an elective polyp removal: how would you handle anticoagulation perioperatively?, and a patient presents with an ischemic stroke because of atrial fibrillation: how soon would you start anticoagulation for secondary stroke prevention? The article summarizes the related literature and discusses the pros and cons of each choice.

Summary
The available evidence is limited; we need to individualize our approach according to the specific characteristics of our patients, and share the decision process with our patients and their proxies, taking strongly into consideration their values and preferences.

Keywords
anticoagulation, hemorrhage, ischemic stroke, stroke, thromboembolism

INTRODUCTION

Right after the end of the Trojan War about 30 centuries ago, Odysseus started his 10-year long journey back to Ithaki, a magnificent journey full of epic adventures wonderfully described by Homer in Odyssey. Among other challenges, Odysseus and his crew had to face two dreadful sea monsters, Scylla and Charybdis, which were located very close to each other in a narrow sea passage forming an inescapable trap: attempting to avoid one of them would bring you fatally close to the other. Scylla had 12 long-neck heads, each with three jaws containing three rows of sharp teeth, whereas Charybdis could generate huge whirlpools capable of dragging a ship underwater. Since then, the idiom 'between Scylla and Charybdis' is used to describe the uncomfortable situation where we need to choose between two evils.

Very few stroke physicians have been lucky enough not to have been confronted with such a dilemma. This article discusses about anticoagulation, a preventive strategy applied to a vast proportion of stroke patients, and with the help of three typical case vignettes tries to focus on three common anticoagulant-related situations, where the stroke physician feels like being between Scylla and Charybdis.

[a]Department of Medicine, Larissa University Hospital, School of Medicine, University of Thessaly, Larissa, Greece, [b]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom and [c]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Correspondence to George Ntaios, MD, MSc (ESO Stroke Medicine), PhD, FESO, Department of Medicine, Larissa University Hospital, School of Medicine, University of Thessaly, Biopolis 41110, Larissa, Greece.
Tel: +30 241 3502888; fax: +30 241 3501557;
e-mail: gntaios@med.uth.gr

Curr Opin Neurol 2015, 28:000–000
DOI:10.1097/WCO.0000000000000283

KEY POINTS

- Often, stroke physicians are required to make difficult clinical decisions with regard to anticoagulation, confronted with the dilemma to choose between the risk of thromboembolism and the risk of bleeding.
- The available evidence is limited, and we need to individualize our approach according to the specific characteristics of our patients.
- We need to share the decision process with our patients and their proxies taking strongly into consideration their values and preferences.

RESTART ANTICOAGULANTS AFTER ANTICOAGULANT-RELATED INTRACRANIAL HEMORRHAGE?

Clinical case vignette: an 80-year-old patient with a history of hypertension, diabetes mellitus, congestive heart failure, and atrial fibrillation on acenocoumarol presents with a right putaminal hemorrhage. International normalized ratio at admission is 1.9 and brain computed tomography (CT) reveals extensive leukoaraiosis. The patient has a good recovery with a modified Rankin scale score of 2 at discharge. Would you restart anticoagulation?

Unfortunately, patients with a history of intracranial hemorrhage (ICH) were excluded from all randomized trials of anticoagulants for stroke prevention, and therefore, related high-quality randomized evidence to guide clinical practice is loudly absent, allowing for considerable debate [1▪,2▪].

Recently, a Danish nationwide cohort study concluded that oral anticoagulation was associated with a significant reduction in ischemic stroke/all-cause mortality rates: the rate of ischemic stroke/systemic embolism and all-cause mortality was 13/100 patient-years compared with 27.3 in the nontreated patients, whereas there was no significant difference in the rate of recurrent ICH (8.6 vs. 8.0, respectively, adjusted hazard-ratio: 0.91, 95% confidence interval 0.56–1.49) [3▪]. Similarly, the CHIRONE study reported that the recurrent ICH rate after restarting vitamin-K antagonists (VKA) was 2.56/100 patient-years during a median follow-up of 16.5 months. Of note, only 0.4 cases/100 patient-years were fatal, and no hemorrhage outside the central nervous system occurred during the follow-up of 778 patient-years [4▪]. Pointing to the same direction, a recent study by the Registry of the Canadian Stroke Network showed that restarting warfarin after ICH did not increase mortality or bleeding in patients with high thrombotic risk [5]. Similarly, no statistically significant difference in outcome between patients who restarted warfarin and patients who did not after a warfarin-associated ICH was reported in a small single-center study of 52 patients [6]. Although all these results seem promising, we need to keep in mind that these are nonrandomized observational studies characterized by the inherent limitations of this type of analysis like – among others – selection bias, collection bias, and inadequate statistical power.

On the other hand, one may argue that an ICH is usually associated with more severe clinical presentation and worse outcome compared with an atrial fibrillation-related ischemic stroke, with approximately 50% case fatality rate at 1 month in the former and 30% in the latter case [7,8]. Therefore, even if the risks of recurrent ICH and ischemic stroke were to be comparable during the follow-up of a patient with an anticoagulant-related ICH, the overall clinical outcome might be poorer in patients who suffer an recurrent ICH compared with patients who suffer an ischemic stroke; in this context, someone may prefer to risk a (possibly milder) ischemic stroke by not restarting anticoagulants rather than a (possibly more severe) recurrent ICH recurrence by restarting anticoagulants.

The quality of available data is reflected in the related guidelines: recently, the authors of the GRADE-based recommendations of the European Stroke Organization about spontaneous ICH management refrained from stating recommendations about whether to restart anticoagulation in an anticoagulant-related ICH in view of the very low quality of evidence [9▪▪,10]. On the contrary, the recent American Heart Association/American Stroke Association provided a class II recommendation to avoid warfarin in lobar ICH and suggested that anticoagulation after nonlobar ICH and antiplatelet monotherapy after any ICH might be considered [11▪▪].

Obviously, until more evidence is available, we need tools to help us individualize our choice based on the specific patient's profile, using risk stratification schemes, such as the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores which predict the thromboembolic and bleeding risks in the long run, both in atrial fibrillation and the nonatrial fibrillation populations [12–16]. Thus, one may consider restarting anticoagulants in patients with high thrombotic risk (e.g., a $CHADS_2 \geq 4$ or a CHA_2DS_2-VASc ≥ 4) and low/moderate bleeding rate (e.g., HAS-BLED ≤ 3). Indeed, the HAS-BLED score is the only bleeding risk score that is predictive of ICH [17]. However, such cases may not be so

common given that certain factors like age, hypertension, and previous stroke are common for both outcomes and most patients with high thrombotic risk have also high risk for bleeding [18,19]. Another parameter to consider could be leukoaraiosis, which is associated with a significantly higher risk for ICH, and in this context, restarting anticoagulants in ICH patients with extensive leukoaraiosis may be associated with increased risk for recurrent ICH [20]. Still, at the same time, leukoaraiosis is an independent predictor also for ischemic stroke both in the atrial fibrillation and nonatrial fibrillation population [21▪].

If the choice of restarting anticoagulation after an anticoagulant-related ICH is preferred, one may consider using one of the non-VKA oral anticoagulants (NOACs, previously referred to as new or novel OACs [22▪▪]), that is, apixaban, dabigatran, edoxaban, or rivaroxaban instead of a VKA. All NOACs were shown to be at least as effective as warfarin both for primary and secondary stroke prevention in atrial fibrillation patients, and significantly safer with an important reduction of the risk for ICH [23,24▪]. Still, one may keep in mind that the superior safety profile of the NOACs over warfarin has not been confirmed in patients with a history of ICH, and therefore, it should be regarded only as an extrapolation of the safety profile in non-ICH atrial fibrillation patients. Although it seems rational to extrapolate this conclusion in the ICH population, it could prove wrong at the end as it was also the case for dabigatran in stroke prophylaxis in patients with mechanical heart valves [25].

Another option with regard to the question of restarting anticoagulants in a patient with an anticoagulant-related ICH could perhaps be to simply escape the question of restarting anticoagulants: the closure of left atrial appendage (LAAC) may be considered as a means to reduce the risk of atrial fibrillation-related ischemic stroke avoiding anticoagulants. Intense research is performed in this area and a recent meta-analysis showed that LAAC resulted in improved rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared with warfarin [26▪]. Still, patients treated with LAAC need indefinite treatment with an antiplatelet drug, which is associated with increased ICH risk.

The brave ones who will decide for restarting anticoagulants in an ICH patient will immediately face another equally challenging question: how soon to restart? Again, the quality of data is low, and several timings have been suggested ranging from 14 days to 30 weeks [27,28].

MANAGEMENT OF ANTICOAGULATION DURING ELECTIVE INTERVENTIONAL PROCEDURES: BURNING DOWN THE BRIDGE?

Clinical case vignette: 7 months after an atrial fibrillation-related stroke, a 76-year-old patient on acenocoumarol is diagnosed with iron-deficiency anemia because of a colonic polyp, which is scheduled for removal in 2 weeks. How would you handle anticoagulation perioperatively?

This is not a rare scenario: approximately one-quarter of the patients in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial underwent an invasive procedure during the mean follow-up of 2 years, with the most common ones being implantation of pacemaker or implantable cardioverter defibrillator, dental procedures, and cataract removal [29]. Some of them, such as dental, dermatologic, and ophthalmologic procedures, are associated with low bleeding risk and anticoagulation may be continued through the procedure [30]. Still, many procedures carry a higher bleeding risk and the treating physician may have to consider de-escalating or even withdrawing anticoagulation periprocedurally with the cost of increasing further the risk of a thromboembolic event. The patient presented in the case vignette is already at high thromboembolic risk taking into consideration the high $CHADS_2$ score ($\geq$3) and that approximately 10% of atrial fibrillation-related strokes recur within the first year [31].

A strategy used in approximately one-quarter of anticoagulation interruptions [32▪] is 'bridging': VKAs are typically withdrawn 5 days before the procedure and restarted 24–48 h after the procedure depending on the bleeding risk of both the procedure and the patient. In the interim, the patient is exposed to higher risk of thromboembolism because of the temporary VKA interruption, and therefore, low-molecular-weight heparin is used to minimize the period that the patient is not anticoagulated.

Although bridging has been a common approach for decades, supporting evidence was not of high quality, and therefore, the strength of recommendations has been weak [33]. During the last years, accumulating observational studies suggested that bridging with low-molecular-weight heparin may not be the optimal strategy. In 2012, a meta-analysis of 34 studies of periprocedural heparin bridging, including 12 278 VKA-treated patients showed that bridging was associated with increased risk of bleeding and similar risk of thromboembolism compared with no bridging [34]. Pointing to the same direction, the outcomes registry for better informed treatment of atrial fibrillation (ORBIT

registry) showed recently that bleeding and the composite event consisting of myocardial infarction, stroke, systemic embolism, major bleeding, hospitalization, or death within 30 days was more frequent in patients treated with bridging [32▪]. Still, stronger evidence from randomized studies was necessary to guide better-informed decisions, and this became available recently with the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial results: in 1884 warfarin-treated atrial fibrillation patients randomized to bridging with 100 IU of dalteparin/kg of body weight or no bridging during an elective intervention, the approach of no bridging was noninferior to bridging for the prevention of arterial thromboembolism (0.4 vs. 0.3%, respectively, $P = 0.01$ for noninferiority) and reduced the risk of major bleeding (1.3 vs. 3.2%, respectively, $P = 0.05$ for superiority) suggesting a net clinical benefit in favor of the no-bridging strategy [35▪▪]. Further, data will become available when the Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism (PERIOP 2) trial is completed, especially with regard to patients with mechanical valve who were not included in the BRIDGE trial (http://clinicaltrials.Gov/ct2/show/nct00432796, accessed 11 August 2015). Recently, the BRIDGE or Continue Coumadin for Device Surgery Randomized Controlled (BRUISE CONTROL) Trial showed that compared with bridging therapy with heparin, a strategy of continued warfarin treatment at the time of pacemaker or implantable cardioverter–defibrillator surgery markedly reduced the incidence of clinically significant device-pocket hematoma (16.0% vs. 3.5%, relative risk 0.19, 95% confidence interval 0.10–0.36, $P < 0.001$) [36]. The HAS-BLED score is a good way to predict the risk of bleeding during bridging [37].

Another strategy for the perioperative management of anticoagulation became available during the recent years with the launch of the NOACs for stroke prevention [23]. Apixaban, dabigatran, edoxaban, and rivaroxaban have rapid onset and offset of action and allow for shorter periods of interruption of anticoagulation; in this case, the timing of NOACs interruption needs to be determined taking into consideration the renal function of the patient and the bleeding risk of the procedure, whereas the resumption of NOACs depends on the type of intervention and the consequences of a bleeding complication [30]. Related evidence has already started to accumulate: results from a prospective registry of unselected patients suggested that continuation or short-term interruption of NOACs is a well tolerated strategy for most invasive procedures [38]. The use of a prespecified protocol for the perioperative management of dabigatran appeared effective and feasible [39▪]. On the contrary, two studies investigating the role of dabigatran in patients undergoing catheter ablation for atrial fibrillation yielded inconsistent results [40,41]. Clearly, more data are needed to confirm the safety and efficacy of the NOACs as a well tolerated and efficacious strategy for the perioperative management of anticoagulation.

ANTICOAGULATION AFTER ISCHEMIC STROKE: HOW SOON (OR LATE)?

Clinical case vignette: an 82-year-old woman with a history of hypertension and diabetes mellitus presents with sudden onset of aphasia and right hemiparesis secondary to newly diagnosed atrial fibrillation; the National Institutes of Health Stroke Scale (NIHSS) score at admission is 13, and brain CT shows diffuse left hemispheric oedema and extensive leukoaraiosis. How soon after the event would you anticoagulate this patient for secondary stroke prevention?

Approximately, 1% of all patients with acute atrial fibrillation-related ischemic stroke will be complicated by a recurrent ischemic stroke within the first week after the index event [31]. In this context, immediate anticoagulation with heparin was a common practice in the past to prevent early recurrent ischemic stroke in atrial fibrillation patients but, at the same time, it was also a frequent debate [42,43]. Later, meta-analyses showed that immediate anticoagulation with heparin in cardioembolic strokes did not significantly reduce the risk for recurrent ischemic stroke, whereas, at the same time, it increased substantially the risk for hemorrhagic transformation, of the infarcted brain tissue [44,45]. In addition, a recent Cochrane meta-analysis which included also oral anticoagulants pointed to the same direction: early anticoagulation reduced recurrent ischemic strokes, but increased the risk for intracranial and extracranial hemorrhage [46▪]. As a result, immediate anticoagulation is not routinely used nowadays for secondary stroke prevention in patients with cardioembolic stroke and such patients are treated with acetylsalicylic acid during the early days after the event until they are passed to an anticoagulant [47].

Ironically, although prevention of recurrent cardioembolism is the reason which warrants anticoagulation as soon as possible in a patient with atrial fibrillation-related stroke, at the same time cardioembolism is one of major predictors of hemorrhagic transformation, directly increasing its risk

by more than five-fold [48]. In addition, cardioembolism increases the risk for hemorrhagic transformation also indirectly, given that cardioembolic strokes are typically associated with large brain lesions which increase the risk for hemorrhagic transformation by more than 12-fold [48].

In view of the paucity of prospective randomized data, official guidelines refrain from providing detailed recommendations about the optimal moment to start anticoagulation in a patient with atrial fibrillation-related stroke and suggest that it is reasonable to initiate oral anticoagulation within 14 days for most stroke patients with atrial fibrillation, and delay anticoagulation for more than 14 days in patients with high risk for hemorrhagic transformation, such as large infarct, hemorrhagic transformation at initial CT scan, uncontrolled hypertension, and hemorrhagic tendency [49▪▪]. Recently, another approach was suggested, the 1–3–6–12 day rule, with initiation of anticoagulation after 1 day in patients with a transient ischemic attack; after 3 days in small, nondisabling infarcts; after 6 days in moderate strokes; and after 12 days in large infarcts [50▪▪]. This suggestion provides a more detailed guidance but, again, it needs to be emphasized that it is based on clinical opinion.

The patient of our vignette has a CHA_2DS_2-VASc score of 7, which corresponds to a high annual stroke risk of approximately 10%. In this context, anticoagulation to prevent ischemic stroke recurrence is warranted in this patient as soon as possible. On the other hand, our patient has a HAS-BLED score of 3, which corresponds to a high bleeding risk ranging between 4.9 and 19.6%, which in the early poststroke period may be manifested as a hemorrhagic transformation of the infarcted tissue: this is not a rare complication as it involves approximately 9% of patients with acute ischemic stroke [48]. One may consider using these scores to guide the clinical decision; unfortunately, we have no validation as yet of the CHA_2DS_2-VASc and the HAS-BLED scores in the early poststroke period. Although it is rational to expect that the thromboembolic and bleeding risk of a patient functions as a continuum, research is warranted to validate these scores in the early poststroke period, or develop new scores to help us estimate the patient thromboembolic and bleeding risks and guide our clinical decisions.

In addition, one may consider using other tools to estimate the thromboembolic or the bleeding risk of the patient. Such a tool could be the use of transesophageal echocardiogram or cardiac CT to search for left atrial thrombi or spontaneous echo contrast: absence of these findings may give the physician and the patient a short but valuable time allowance of refraining from anticoagulation. Another tool could be the use of biomarkers like the matrix metalloproteinases, which were shown to be correlated with disrupted permeability of the blood–brain barrier and hemorrhagic transformation in experimental stroke models [51]. Also, MRI could be elaborated as a means to estimate the risk for hemorrhagic transformation [52]. However, these may be difficult to apply broadly at least in limited-resource settings, and further, studies need to investigate whether the information yielded by these examinations can reliably guide our clinical decisions about the time of initiation of anticoagulation in patients with atrial fibrillation-related stroke.

Finally, regardless of how soon (or late) one decides to start anticoagulation after an atrial fibrillation-related stroke, it seems rational to start anticoagulation with a NOAC at the low dose (i.e., 2.5 mg twice daily for apixaban, 110 mg twice daily for dabigatran, 30 mg once daily for edoxaban, and 15 mg once daily for rivaroxaban) rather than a VKA, at least for the early period after the stroke: given the better safety profile of the NOACs compared with warfarin [23], it could be expected that the NOACs will be associated with lower rates of hemorrhagic transformation. However, this is not evidence based and remains to be confirmed as the randomized controlled trials of the NOACs did not include patients in the early poststroke period. Ongoing registries will provide some answers in the near future.

CONCLUSION

Odysseus was aware that there was no easy way out of the trap set by Scylla and Charybdis. He was confronted with a difficult dilemma: either he would navigate his ship close to Scylla with the risk that the monster would capture some of its crew members, or he would pass close to Charybdis with the risk to be sucked in the whirlpool and lose his entire ship and crew. He decided to take the first option, and he managed to get through with the loss of (only) six of his crew members.

Unfortunately, like Odysseus, for the time being we do not have clear answers for the dilemmas presented above with regard to anticoagulation in stroke patients for two main reasons: first, because the balance between the thromboembolic and bleeding risk is very delicate and the safe path between Scylla and Charybdis is very narrow, if any; second, because the available evidence is currently scarce and we lack validated tools to compare

reliably the two risks. On the other hand, fortunately, research in this area is intense, and hopefully, we shall be able to make better-informed choices sooner or later.

Until then, we need to individualize our approach according to the specific characteristics of our patients, and share the decision process with our patients and their proxies taking strongly into consideration their values and preferences.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

G.N.: Speaker honoraria from Boehringer-Ingelheim and Bayer. G.Y.H.L.: Guideline membership/reviewing: ESC Guidelines on Atrial Fibrillation, 2010 and Focused Update, 2012; ESC Guidelines on Heart Failure, 2012; American College of Chest Physicians Antithrombotic Therapy Guidelines for Atrial Fibrillation, 2012; NICE Guidelines on Atrial Fibrillation, 2006 and 2014; NICE Quality Standards on Atrial Fibrillation 2015; ESC Cardio-oncology Task Force, 2015; ESC Working Group on Thrombosis position documents (2011). Chairman, Scientific Documents Committee, European Heart Rhythm Association (EHRA). Reviewer for various guidelines and position statements from ESC, EHRA, NICE etc. Steering Committees/trials: Includes steering committees for various Phase II and III studies, Health Economics and Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc. Editorial Roles: Editor-in-Chief (clinical), Thrombosis and Haemostasis; Associate Editor, Europace; Guest Editor, Circulation, American Heart Journal. Consultant/Advisor/Speaker: Consultant for Bayer/Jensen J&J, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Ricci S, Pistoia F, Carolei A, Sacco S. Restarting oral anticoagulants after ■ intracerebral hemorrhage: cons. Intern Emerg Med 2015; 10:5–7.

An interesting debate on restarting oral anticoagulants after ICH.

2. Ntaios G. Restarting oral anticoagulants after intracerebral hemorrhage: pros. ■ Intern Emerg Med 2015; 10:3–4.

An interesting debate on restarting oral anticoagulants after ICH.

3. Nielsen PB, Larsen TB, Skjoth F, *et al.* Restarting anticoagulant treatment after ■ intracranial haemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality and bleeding: a nationwide cohort study. Circulation 2015; 32:517–525.

A Danish nationwide cohort study about restarting anticoagulants after ICH.

4. Poli D, Antonucci E, Dentali F, *et al.* Recurrence of ICH after resumption of ■ anticoagulation with vk antagonists: CHIRONE study. Neurology 2014; 82:1020–1026.

An Italian study showing that that patients with a history of ICH carry a significant risk of recurrent ICH, when treated with VKA anticoagulation.

5. Claassen DO, Kazemi N, Zubkov AY, *et al.* Restarting anticoagulation therapy after warfarin-associated intracerebral hemorrhage. Arch Neurol 2008; 65:1313–1318.
6. Yung D, Kapral MK, Asllani E, *et al.* Investigators of the Registry of the Canadian Stroke N. Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and mortality risk: the best practice for reinitiating anticoagulation therapy after intracranial bleeding (brain) study. Can J Cardiol 2012; 28:33–39.
7. Sacco S, Marini C, Toni D, *et al.* Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. Stroke 2009; 40:394–399.
8. Sacco S, Stracci F, Cerone D, *et al.* Epidemiology of stroke in Italy. Int J Stroke 2011; 6:219–227.
9. Steiner T, Al-Shahi Salman R, Beer R, *et al.* European Stroke Organisation ■■ (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke 2014; 9:840–855.

The must-read GRADE-based Guidelines of the European Stroke Organisation for the management of spontaneous ICH.

10. Ntaios G, Bornstein NM, Caso V, *et al.* The European Stroke Organisation guidelines: a standard operating procedure. Int J Stroke 2015; 10 ((Suppl A100)):128–135.
11. Hemphill JC 3rd, Greenberg SM, Anderson CS, *et al.* Guidelines for the ■■ management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015; 46:2032–2060.

The must-read Guidelines of the American Heart Association/American Stroke Association for the management of spontaneous ICH.

12. Gage BF, van Walraven C, Pearce L, *et al.* Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004; 110:2287–2292.
13. Gage BF, Waterman AD, Shannon W, *et al.* Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864–2870.
14. Lip GY, Nieuwlaat R, Pisters R, *et al.* Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010; 137:263–272.
15. Pisters R, Lane DA, Nieuwlaat R, *et al.* A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138:1093–1100.
16. Ntaios G, Lip GY, Makaritsis K, *et al.* CHADS(2), CHA(2)S(2)DS(2)-VASc, and long-term stroke outcome in patients without atrial fibrillation. Neurology 2013; 80:1009–1017.
17. Apostolakis S, Lane DA, Guo Y, *et al.* Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. J Am Coll Cardiol 2012; 60:861–867.
18. Apostolakis S, Lane DA, Buller H, Lip GY. Comparison of the CHADS2, CHA2DS2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. Thromb Haemost 2013; 110:1074–1079.
19. Roldan V, Marin F, Manzano-Fernandez S, *et al.* The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol 2013; 62:2199–2204.
20. Lovelock CE, Cordonnier C, Naka H, *et al.* Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies. Stroke 2010; 41:1222–1228.
21. Ntaios G, Lip GY, Lambrou D, *et al.* Leukoaraiosis and stroke recurrence risk ■ in patients with and without atrial fibrillation. Neurology 2015; 84:1213–1219.

An interesting paper about the association between leukoaraiosis and stroke recurrence risk.

22. Husted S, de Caterina R, Andreotti F, *et al.* Nonvitamin K antagonist oral ■■ anticoagulants (NOACs): No longer new or novel. Thromb Haemost 2014; 111:781–782.

An editorial by the European Society of Cardiology Working Group On Thrombosis Task Force On Anticoagulants In Heart Disease about the NOAC acronym.

23. Ntaios G, Papavasileiou V, Diener HC, *et al.* Nonvitamin-k-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. Stroke 2012; 43:3298–3304.

24. Ruff CT, Giugliano RP, Braunwald E, *et al.* Comparison of the efficacy and
■ safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383:955–962.
A thorough meta-analysis of all NOACs for stroke prevention in atrial fibrillation patients.
25. Eikelboom JW, Connolly SJ, Brueckmann M, *et al.* Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013; 369:1206–1214.
26. Holmes DR Jr, Doshi SK, Kar S, *et al.* Left atrial appendage closure as an
■ alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis. J Am Coll Cardiol 2015; 65:2614–2623.
A meta-analysis about the role of lefta atrial appendage closure for stroke prevention in atrial fibrillation patients.
27. Majeed A, Kim YK, Roberts RS, *et al.* Optimal timing of resumption of warfarin after intracranial hemorrhage. Stroke 2010; 41:2860–2866.
28. Aguilar MI, Hart RG, Kase CS, *et al.* Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. Mayo Clin Proc 2007; 82:82–92.
29. Healey JS, Eikelboom J, Douketis J, *et al.* Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: Results from the randomized evaluation of long-term anticoagulation therapy (RE-LY) randomized trial. Circulation 2012; 126:343–348.
30. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood 2012; 120:2954–2962.
31. Ntaios G, Michel P. Temporal distribution and magnitude of the vulnerability period around stroke depend on stroke subtype. Cerebrovasc Dis 2011; 32:246–253.
32. Steinberg BA, Peterson ED, Kim S, *et al.* Use and outcomes associated with
■ bridging during anticoagulation interruptions in patients with atrial fibrillation: Findings from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF). Circulation 2015; 131:488–494.
Another excellent analysis from the ORBIT-atrial fibrillation registry.
33. Douketis JD, Spyropoulos AC, Spencer FA, *et al.* Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141:e326S–e350S.
34. Siegal D, Yudin J, Kaatz S, *et al.* Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation 2012; 126:1630–1639.
35. Douketis JD, Spyropoulos AC, Kaatz S, *et al.* Perioperative bridging anti-
■■ coagulation in patients with atrial fibrillation. N Engl J Med 2015; 373:823–833.
An important randomized controlled trial showing that, perhaps, bridging is not the answer for perioperative management of anticoagulants.
36. Birnie DH, Healey JS, Essebag V. Device surgery without interruption of anticoagulation. N Engl J Med 2013; 369:1571–1572.
37. Omran H, Bauersachs R, Rubenacker S, *et al.* The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation. Results from the national multicentre BNK online bRiDging REgistRy (BORDER). Thromb Haemost 2012; 108:65–73.
38. Beyer-Westendorf J, Gelbricht V, Forster K, *et al.* Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J 2014; 35:1888–1896.
39. Schulman S, Carrier M, Lee AY, *et al.* Perioperative management of dabiga-
■ tran: a prospective cohort study. Circulation 2015; 132:167–173.
An interesting study about the use of dabigatran perioperatively.
40. Lakkireddy D, Reddy YM, Di Biase L, *et al.* Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. J Am Coll Cardiol 2012; 59:1168–1174.
41. Bassiouny M, Saliba W, Rickard J, *et al.* Use of dabigatran for periprocedural anticoagulation in patients undergoing catheter ablation for atrial fibrillation. Circ Arrhythm Electrophysiol 2013; 6:460–466.
42. Sandercock P. Full heparin anticoagulation should not be used in acute ischemic stroke. Stroke 2003; 34:231–232.
43. Caplan LR. Resolved: heparin may be useful in selected patients with brain ischemia. Stroke 2003; 34:230–231.
44. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. Stroke 2007; 38:423–430.
45. Guedes LC, Ferro JM. A systematic review of immediate anticoagulation for ischemic stroke of presumed cardioembolic origin. Stroke 2008; 39:e81–e82.
46. Sandercock PA, Counsell C, Kane EJ. Anticoagulants for acute ischaemic
■ stroke. Cochrane Database Syst Rev 2015; 3:CD000024.
A thorough Cochrane analysis about the use of anticoagulants for acute ischemic stroke.
47. European Stroke Organisation (ESO) Executive Committee ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008; 25:457–507.
48. Paciaroni M, Agnelli G, Corea F, *et al.* Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 2008; 39:2249–2256.
49. Kernan WN, Ovbiagele B, Black HR, *et al.* Guidelines for the prevention of
■■ stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45:2160–2236.
The must-read Guidelines of the American Heart Association/American Stroke Association about the secondary stroke prevention.
50. Heidbuchel H, Verhamme P, Alings M, *et al.* European heart rhythm associa-
■■ tion practical guide on the use of new oral anticoagulants in patients with nonvalvular atrial fibrillation. Europace 2013; 15:625–651.
An excellent practical guide on the use of NOACs in patients with atrial fibrillation.
51. Jia L, Chopp M, Zhang L, *et al.* Erythropoietin in combination of tissue plasminogen activator exacerbates brain hemorrhage when treatment is initiated 6 h after stroke. Stroke 2010; 41:2071–2076.
52. Alvarez-Sabin J, Maisterra O, Santamarina E, Kase CS. Factors influencing haemorrhagic transformation in ischaemic stroke. Lancet Neurol 2013; 12:689–705.